Labeling Guidance
Revised 12/93

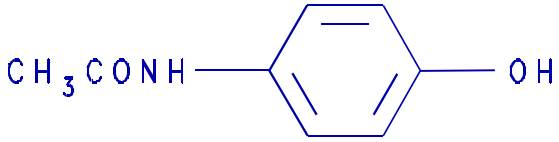
CIII

ACETAMINOPHEN, ASPIRIN AND CODEINE PHOSPHATE TABLETS
ACETAMINOPHEN, ASPIRIN AND CODEINE PHOSPHATE CAPSULES

DESCRIPTION

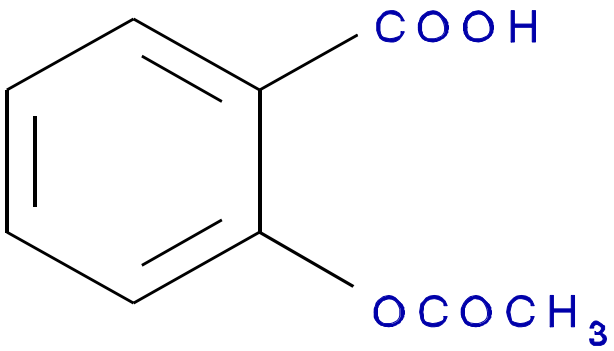
Acetaminophen, aspirin and codeine is supplied in tablet/capsule form for oral administration.

Acetaminophen, 4'-hydroxyacetanalide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



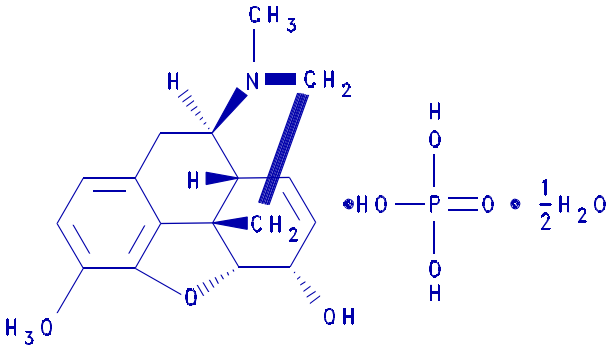
$C_8H_9NO_2$ MW = 151.16

Aspirin, benzoic acid, 2-(acetyloxy)-, is a non-opiate, analgesic, anti-inflammatory and antipyretic agent. It occurs as a white, crystalline tabular or needle-like powder and is odorless or has a faint odor. It has the following structural formula:



$C_9H_8O_4$ M.W. = 180.16

Codeine phosphate, 7,8-didehydro-4,5 α-epoxy-3-methoxy-17-methylmorphinan-6 α-ol phosphate (1:1) (salt) hemihydrate, a white crystalline powder, is a narcotic analgesic and antitussive. It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ MW = 406.37

Each tablet/capsule contains:

Acetaminophen	____ mg
Aspirin	____ mg
Codeine Phosphate (Warning: May be habit forming)	____ mg

In addition each tablet/capsule contains the following inactive ingredients:

We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure.

CLINICAL PHARMACOLOGY

This product combines the analgesic effects of a centrally acting analgesic, codeine, with the peripherally acting analgesics, acetaminophen and aspirin.

Pharmacokinetics: The behavior of the individual components is described below.

Codeine : Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

See OVERDOSAGE for toxicity information.

Acetaminophen : Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

Aspirin : The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of aspirin prior to absorption.

During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids, including fetal tissues, breast milk, and the central nervous system (CNS). Highest concentrations are found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50% to 80% of the salicylic acid and its metabolites are loosely bound to plasma proteins.

The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for aspirin is about 12 minutes and for salicylic acid and/or total salicylates is about 3.0 hours.

The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products. The renal clearance is greatly augmented by an alkaline urine as is produced by concurrent administration of sodium bicarbonate or potassium citrate.

The biotransformation of aspirin occurs primarily in the hepatocytes. The major metabolites are salicyluric acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%).

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Acetaminophen, aspirin and codeine phosphate tablets/capsules are indicated for the relief of mild to moderately severe pain.

CONTRAINDICATIONS

This product is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to any component of this product.

2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage).

3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.

4. Peptic ulcer or other serious gastrointestinal lesions.

WARNINGS

Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Codeine is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS

General: This product should be prescribed with caution in certain special-risk patients, such as the elderly or

debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, prostatic hypertrophy or coagulation disorders.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that this product contains aspirin and should not be taken by patients with an aspirin allergy.

Codeine may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Codeine may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Caution patients with a predisposition for gastrointestinal bleeding that concomitant use of aspirin and alcohol may have an additive effect in this regard.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

This drug may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.

2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of this product exceeds maximum recommended daily dosage.

3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and in the case of methotrexate, also reducing its excretion.

4. Nonsteroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing to additive effects.

5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

This product may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions: Aspirin : Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamicoxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine : Codeine may increase serum amylase levels.

Acetaminophen : Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility.

No adequate studies have been conducted in animals to determine whether acetaminophen and codeine have a potential for carcinogenesis or mutagenesis. No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for impairment of fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy:
Teratogenic Effects: Pregnancy Category C:
A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogeneses in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no adequate and well-controlled studies in pregnant women. This product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:
Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth,

neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate.

Nursing Mothers: Acetaminophen, aspirin and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known.

Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and abdominal pain. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse drug events which may be borne in mind as potential effects of the components of this product are: allergic

reactions, euphoria, dysphoria, constipation, pruritus, rash, thrombocytopenia, agranulocytosis, occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity (when aspirin is taken in high doses for prolonged periods), impaired urate excretion, and hepatitis.

At higher doses codeine has most of the disadvantages of morphine including respiratory depression.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Acetaminophen, aspirin and codeine phosphate tablets/capsules are classified as a Schedule III controlled substance.

Abuse and Dependence: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

OVERDOSAGE

Following an acute overdosage, toxicity may result from codeine, acetaminophen or aspirin.

Signs and Symptoms:
Codeine: Toxicity from codeine poisoning includes the opioid triad of: pinpoint pupils, depression of respiration, and loss of consciousness. Convulsions may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise.

Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Aspirin: Hyperpnea, acid-base disturbances with development of metabolic acidosis, vomiting and abdominal pain, tinnitus, hyperthermia, hypoprothrombinemia, restlessness, delirium, and convulsions.

Treatment: A single or multiple overdose with acetaminophen, aspirin and codeine is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Treatment consists primarily of reversal of the effects of codeine and acetaminophen, and the correction of the acid-base imbalance due to salicylism.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose injection.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone

hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of codeine may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels fours or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Toxic Doses (for adults):

Acetaminophen: toxic dose 10 g
Aspirin: toxic blood level greater than 30 mg/100 mL
Codeine: toxic dose 240 mg

Lethal Doses (for adults):

Aspirin: 10 to 30 g
Codeine: 0.5 to 1 g

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. It should be kept in mind, however, that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in children would have similar effects.

The dose of this combination product is limited by the amount of codeine phosphate per tablet/capsule. For adults, a single dose of codeine phosphate should not exceed 60 mg. For children, the usual recommended single dose is 0.5 mg/kg.

[Choose the appropriate statement(s) based on the amount of codeine phosphate in the product:]

15 mg or 30 mg:	The usual adult dosage is one or two tablets/capsules every four hours as needed.
60 mg:	The usual adult dosage is one tablet/capsule ever four hours as needed.

HOW SUPPLIED

- Established name and strength
- Packaging
- Shape, color, coating, scoring, etc...
- Special handling and storage conditions

Manufacturer/Distributor's name and place of business.
Date of latest revision.